NEPHROTIC SYNDROME
LEARNING OBJECTIVES

• Explain the pathophysiology in Nephrotic syndrome
• Define Nephrotic syndrome
• Classify the etiology of Nephrotic syndrome
• Describe clinical features of Nephrotic Syndrome
• Clinically differentiate Nephrotic syndrome from Acute Nephritis
• Plan investigations of Nephrotic syndrome
• Plan the treatment and follow up of Typical Nephrotic syndrome
• Discuss the complications of nephrotic syndrome
PATHOPHYSIOLOGY
GLOMERULUS, PODOCYTE FOOT PROCESS AND BASEMENT MEMBRANE
ALBUMINURIA IN NEPHROTIC SYNDROME

• Normal Glomerular basement membrane (GBM) is *negatively* charged
• In Minimal Change Nephrotic Syndrome the GBM *loses* its negative charges
• Loss of negative charge leads to *inability to repulse* small negative charged proteins like albumin
• This leads to an *increased loss of albumin* in urine in spite of there being no mechanical damage to the membrane.
DAMAGE IS IMMUNOLOGICAL

Defective T cell mediated immunity

Active interleukins: IL2, IL1, IL6

Circulating factors
PATHO-PHYSIOLOGY OF EDEMA:

- Increased glomerular permeability to albumin
  - Albuminuria
  - Hypoalbuminemia
    - Decreased plasma oncotic pressure
      - Movement of water from intravascular space to interstitium
        - Hypovolemia
          - Nonosmotic ADH release
            - Renin-angiotensin-aldosterone system
              - Renal water and sodium retention
                - EDEMA
          - Sympathetic nervous system

Under-fill theory
PATHO-PHYSIOLOGY OF EDEMA

Primary renal sodium retention

Increased blood volume

Increased blood pressure

Altered Starling forces at local tissue level

EDEMA

Suppression of renin-angiotensin system


DEFINITION
DEFINITION: NEPHROTIC SYNDROME

A renal glomerular disorder characterized by
Massive proteinuria
Hypoalbuminemia
Hypercholesterolemia and
With or without edema.
INCIDENCE

2.7 new cases per 100,000 children per year
ETIOLOGY
ETIOLOGY

PRIMARY

• Idiopathic Nephrotic Syndrome
  – Minimal Change Nephrotic Syndrome
    • 80%, Under age 7 years
    • 50%, age 7-14 years
  – Focal Segmental Glomerulosclerosis, Membrano-proliferative glomerulonephritis, Membranous glomerulonephritis
• Congenital Nephrotic Syndrome

SECONDARY

• Connective Tissue Disorders
  – SLE
  – Henoch-Schonlein Purpura
• Infections
  – Hepatitis B/C
  – Malaria
• Miscellaneous
  – Drugs
  – Malignancies
  – Bee stings
CLINICAL FEATURES
CLINICAL FEATURES: SYMPTOMS

• Age: 6 months to 7 years

• Insidious onset

• Edema
  Periorbital/Anasarca
  More in the mornings

• Oliguria: Follows Edema

• Sex: Male
PERIORBITAL EDEMA
ANASARCA:
ASCITES, PEDAL EDEMA, VULVAL/PENILE/SCROTAL EDEMA
PITTING PEDAL EDEMA
VISIBLE VEINS WITH MASSIVE ASCITES
Edema
- Pitting
- Bilateral Pedal
- Sacral
- Periorbital
- Scrotum
- Abdomen
- Ascites
- Pleural effusion

• Infection
  - Fever
  - Peritonitis
  - Cellulitis

• Normotensive
  - Shock
NEPHROTIC SYNDROME VERSUS ACUTE GLOMERULONEPHRITIS
## CLINICAL DIFFERENTIATION

<table>
<thead>
<tr>
<th>Nephrotic Syndrome (MCNS)</th>
<th>Acute Glomerulonephritis (Post Streptococcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insidious onset</td>
<td>Acute onset</td>
</tr>
<tr>
<td>Edema, especially anasarca</td>
<td>Hematuria, Oliguria initially</td>
</tr>
<tr>
<td>Oliguria follows</td>
<td>Edema follows</td>
</tr>
<tr>
<td>Hypovolemic Shock</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Ascites</td>
<td>Seizures</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Congestive cardiac failure</td>
</tr>
</tbody>
</table>

IAP UG Teaching slides 2015-16 21
ATYPICAL FEATURES

Gross hematuria
Hypertension
Steroid resistance
Hypo-complementememia
Joint involvement
Skin rash
Renal failure
INVESTIGATIONS
INVESTIGATIONS: ROUTINE

• Hematology
  – Hb
  – Total WBC Count
  – Differential Count

• Urine
  – Protein Dipstick (Tetrabromophenol blue)
  – Sugar
  – Microscopy
  – Culture/Sensitivity

• Rule out Anemia
  • Rule out Infections
  • Detect Proteinuria
  • Detect Lipiduria
  • Detect Urinary tract infection
INVESTIGATIONS: ROUTINE CONTD.

Biochemistry
– Blood Urea
– Serum Creatinine
– Serum Electrolytes
– Serum Cholesterol
URINE FOR PROTEINS

Qualitative techniques:

Turbidometric method

Denaturation and precipitation of urinary protein by acid and heat

Turbidity compared to standards

Detects all proteinuria

False positives: contrast agents, high levels of antibiotics
URINE DIPSTICK ESTIMATION

<table>
<thead>
<tr>
<th>Dipstick</th>
<th>Protein Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>0 mg/dl</td>
</tr>
<tr>
<td>Trace</td>
<td>15-30 mg/dl</td>
</tr>
<tr>
<td>1+</td>
<td>30-100 mg/dl</td>
</tr>
<tr>
<td>2+</td>
<td>100-300 mg/dl</td>
</tr>
<tr>
<td>3+</td>
<td>300-1000 mg/dl</td>
</tr>
<tr>
<td>4+</td>
<td>&gt; 1000 mg/dl</td>
</tr>
</tbody>
</table>
LIPID BODIES IN URINE
INVESTIGATIONS: SPECIFIC

- Urine
  - 24 hour Urine Protein
  - Urine Protein:Creatinine Ratio

- Serum Complement
- HbsAg

- Confirm Nephrotic range proteinuria (> 1 gm/sqm/24 hr; Urine Pr: Cr ratio > 2.0)

- Only if atypical features are present
- HBV is an etiology
INVESTIGATIONS: SPECIFIC CONTD.

• Mantoux test
• Chest X-Ray
• Renal Biopsy

• Pre-requisite for initiating treatment with corticosteroids

• Atypical, Congenital, steroid resistance
LABORATORY DIFFERENTIATION

<table>
<thead>
<tr>
<th>Nephrotic Syndrome (MCNS)</th>
<th>Acute Glomerulonephritis (Post Streptococcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urine Protein</strong> 3+ to 4+</td>
<td><strong>Urine Protein</strong> 1+ to 2+</td>
</tr>
<tr>
<td>Urine Lipid bodies</td>
<td><strong>Urine RBCs</strong></td>
</tr>
<tr>
<td><strong>24 Urine Protein &gt;1 gm/sqm/24hr</strong></td>
<td><strong>Urine RBC Casts</strong></td>
</tr>
<tr>
<td><strong>Urine Pr: Cr ration &gt; 2.0</strong></td>
<td>Azotemia</td>
</tr>
<tr>
<td><strong>Serum Albumin &lt; 2.5 gm/dl</strong></td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td><strong>Serum Cholesterol &gt; 250 mg/dl</strong></td>
<td>Elevated ASLO titre</td>
</tr>
<tr>
<td></td>
<td>Hypocomplementemia</td>
</tr>
</tbody>
</table>
DIAGNOSIS:
THE TRIAD OF NEPHROTIC SYNDROME

Edema

Proteinuria
(Urine protein >2 gm/m²/day)

Hypoalbuminemia
(Serum albumin < 2.5 g/dl)

Hypercholesterolemia
(Serum Cholesterol >250 mg/dl)
TREATMENT
TREATMENT : FIRST STEPS

Confirm diagnosis
Confirm Typical versus Atypical features
Rule out Infections
Rule out Tuberculosis
Rule out Complications
Educate parents/child
TREATMENT

General
Supportive
Edema management
Complication management
Vaccination

Specific
Corticosteroids
SUPPORTIVE THERAPY

**Diet:**
- 1.5-2gm / kg of protein
- Normal Calories
- Fat not >30% of calories
- Salt restriction if edematous

**Edema:**
- Corticosteroids
- Water Immersion therapy
- Diuretics / Albumin infusion

**Vaccination**
- No live vaccines
- Give pneumococcal and H influenza vaccines
First Episode of Nephrotic Syndrome
Absence of hypertension, hematuria, azotemia

Prednisolone 2 mg/kg daily for 6 weeks, followed by 1.5 mg/kg on alternate days for 6 weeks

- Infrequent relapses
- Frequent relapses
  - Steroid dependence
    - Refer for evaluation
    - Alternate day prednisolone to maintain remission; assess steroid threshold
    - Threshold < 0.5-0.7 mg/kg on alternate days
      - Alternate day prednisolone for 9-18 months
    - Threshold > 0.5-0.7 mg/kg on alternate days or steroid toxicity
      - Levamisole
      - Cyclophosphamide, Tacrolimus, Mycophenolate mofetil, Cyclosporin

- Steroid resistance
  - Refer for evaluation
  - Therapy based on renal biopsy findings
CORTICOSTEROIDS: FIRST EPISODE

- Prednisolone
  - 60 mg / sqm / 24 hr or 2 mg /kg / 24 hr
  - Divided doses
  - 6 weeks

Then.....
- 40 mg / sqm / alternate days or 1.5 mg /kg / alternate days
- Once a day dose
- 6 weeks

Then....
- May taper off
CORTICOSTEROIDS: RELAPSE

• Prednisolone
  – 60 mg / sqm / 24 hr or 2 mg /kg / 24 hr
  – Divided doses
  – Till remission (2 weeks)

Then.....
  – 40 mg / sqm / alternate days or 1.5 mg /kg / alternate days
  – Once a day dose
  – 4 weeks
COMPLICATIONS
COMPLICATIONS

Massive edema
Malnutrition
Infections
  – Peritonitis
  – Cellulitis
  – Pneumonia
  – UTI
Thromboembolism
Hypotension
Shock

• Hypothyroidism
• Iron Deficiency Anemia
• Vitamin D deficiency
• Growth failure
• Steroid toxicity
PERITONITIS

Peritoneal fluid:
• >250 cells/cmm
  or >50% neutrophil
• Gram stain
• Culture

Early Cellulitis
Asymmetry of lower limbs in Deep vein thrombosis

Cerebro venous thrombosis
With right monoparesis
Prolonged capillary filling rate
In hypovolemic shock

Short stature and cushingoid features
Infections: Antibiotics+ stress dose steroids (0.5mg/kg/day for 5 days)

Hypovolemia: Fluids/Albumin infusion

Thrombosis: Anticoagulant therapy
PARENTAL COUNSELLING

• Urine examination for protein at home using dipstick, sulfosalicylic acid or boiling test.
• Daily urine examination in the morning during a relapse, during intercurrent infections or if there is even mild periorbital puffiness.
• The frequency of urine examination is reduced, to once or twice a week, during remission.
PARENTAL COUNSELLING CONTD.

• Diary for results of urine protein examination, medications received and intercurrent infections.
• Ensure normal activity and school attendance.
• Appropriate immunization and other measures for protection against infections.
FOLLOW UP
**RELAPSE OR REMISSION**

**Relapse**
Urine albumin $\geq$++ in an early morning sample for 3 consecutive days

**Remission**
Urine albumin nil/trace for 3 consecutive days
FOLLOW UP

Steroid Sensitive Nephrotic Syndrome
In remission even after stoppage of steroids

Steroid Dependent Nephrotic Syndrome
Relapse during tapering off or within 14 days of stopping steroids

Steroid Resistant Nephrotic Syndrome
No remission even after 4 weeks of high dose steroids
OTHER MEDICATIONS USED IN STEROID DEPENDENT AND RESISTANT PATIENTS

Cyclophosphamide

Chlorambucil

Levamisole

Cyclosporine

Tacrolimus
CONCLUSION

Nephrotic syndrome is the commonest glomerular disease in children
It has a chronic clinical course with recurrent episodes of edema
Response to steroid therapy has a good prognosis
Close follow up of the child and monitoring for side effects of immunosuppressants is important
EXAM QUESTIONS

Describe clinical features and management of a child with 1st episode nephrotic syndrome

Define steroid dependence/resistance

Enumerate the complications of Nephrotic syndrome
EXAM QUESTIONS

Write a note on:

• Steroid toxicity
• Infections in nephrotic syndrome
• Urine protein estimation
• Differences between nephritis and nephrotic syndrome
THANK YOU